UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/241,347	02/02/1999	HERMANN BUJARD	BBI-009C4CN	8608

959 7590 09/23/2005

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/241,347	BUJARD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, filed June 29, 2005, is acknowledged. Claims 1, 2, 4, 5, 7-10, 13, 15, and 26-46 are cancelled. Claims 47-85 are newly added.

Claims 47-85 are pending.

Withdrawn Rejections

35 U.S.C. § 112, 1st parag., Written Description

Applicant's arguments, see Applicant's response, pages 12-13, filed, May 25, 2005 with respect to claims 1, 2, 4, 5, 7-10, 13, 15, 26-46, have been fully considered and are persuasive. The rejection of claims 1, 2, 4, 5, 7-10, 13, 15, 26-46 has been withdrawn because the claims have been cancelled.

New/Maintained Rejections

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 47, 54, 55, 64, 66, 69 are provisionally rejected in modified form under 35 U.S.C. 101 as claiming the same invention as that of claims 22, 23, 28, 51-54 of

copending Application No. 09/874,389. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. This rejection has been modified to include additional claims wherein provisional double patenting exists. It is noted that Applicants have not traversed the grounds of rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of cancelled claims 1, 2, 4, 5, 7-10, 13, 15, and 26-46 is maintained over new claims 47-85 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 5,866,755 (2/2/99) for reasons of record set forth in the previous Office Actions of 7/8/99, 9/13/01, 5/21/03, 4/24/04, and 1/11/05. It is noted that Applicants have not traversed the grounds of rejection.

Response to Arguments

It is noted that Applicant's request to hold the obviousness-type double patenting rejection with regards to claims 47-85 of the instant invention as being unpatentable over claims 1-25 of U.S. Patent 5,866,755 in abeyance until the indication of allowable claims was acknowledged April 20, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-85 are rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising in its genome, a tTA expression construct comprising a nucleic acid sequence (SEQ ID NO. 1) encoding tTA^R operably linked to a CMV promoter and a luciferase reporter construct comprising a nucleic acid sequence encoding luciferase operably linked to a tetracycline-responsive P_{hCMV^*} promoter (SEQ ID NO. 8), wherein luciferase activity was detectable in the seven tissues of the double transgenic mice examined: pancreas, kidney, stomach, muscle, thymus, heart, and tongue,

does not reasonably provide enablement for

a non-human transgenic animal comprising in its genome,

a) a transgene construct comprising a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells,

b) the fusion protein comprising a first polypeptide, which is a Tet repressor or mutated Tet repressor that binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein i) the transgene is expressed in cells of the animal at a level sufficient to produce amounts of the fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene, and ii) the level of transcription of the tet operator-linked gene is upon regulation less than the level of transcription prior to regulation by the fusion protein;

a non-human transgenic animal comprising in its genome,

a) a transgene comprising a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

b) said fusion protein comprises a first polypeptide which is a Tet repressor operably linked to a heterologous second polypeptide which inhibits transcription of said tet operator-linked gene in eukaryotic cells,

c) said tet operator-linked gene is expressed at detectable levels in cells of the animal in the presence of tetracycline or an analogue thereof,

d) said transgene is expressed in cells of the animal at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene, and

e) in the absence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator linked gene, wherein the level of expression of the tet operator-linked gene can be upregulated by administering tetracycline or a tetracycline analogue to the animal;

a non-human transgenic animal having a transgene integrated into the genome of the animal and also having a tet operator-linked gene in the genome of the animal wherein:

a) the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

b) said fusion protein comprises a first polypeptide that is a mutated Tet repressor that binds to tet operator sequences in the presence, but not the absence, of tetracycline or a tetracycline analogues, operably linked to a heterologous second polypeptide which inhibits transciprion of said tet operator-linked gene in eukaryotic cells;

c) said tet operator-linked gene is expressed at detectable levels in cells of the animal in the absence of tetracycline or an analogue thereof,

d) said transgnee is expressed in cells of the animal at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene, and

e) in the presence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator-linked gene, wherein the level of expression of the tet operator-linked gene can be upregulated by depleting tetracycline or a tetracycline analogue from the animal,

and

a transgenic non-human animal having atransgene integrated into the genome of the animal, wherein:

a) the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of a tet operator-linked gene,

b) the fusion protein comprises a first polypeptide that is a Tet repressor or a mutated Tet repressor that binds to a tet operator sequence, operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells, and

c) said fusion protein is expressed in cells of the animal.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record stated in Office Actions of 7/8/99, 9/13/01, 5/21/03, 4/24/04, and 1/11/05. It is noted that compared with the previous Office Action, the present scope of enablement is narrower. The scope of the

previous Office Actions was transgenic mice. However, now, the scope has been narrowed to the mice taught in the specification. The scope is narrower because in light of the teachings of Hammer et al., as discussed in the previous Office Actions, an artisan cannot predict what the phenotype is of a transgenic mouse comprising the tet system, wherein any heterologous protein is expressed. Because the art teaches unpredictability in phenotype exhibited by transgenic mice that overexpress heterologous proteins and the specification does not teach an artisan how to overcome the teachings of the art, an artisan would need to determine empirically whether each heterologous protein expressed in a transgenic mouse has a phenotype corresponding to the overexpression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments, pages 10-12 of Applicant's response, filed June 29, 2005, have been fully considered but they are not persuasive.

With regards to the Applicant's argument that "enablement of the claimed invention does not require a skilled artisan to be able to make and use a transgenic animal exhibiting a phenotype (Applicant's response, page 10, part A)," the Examiner does not find the argument persuasive. The art teaches that there are many examples in which transgenic non-human animals have been made and which exhibit no phenotype (e.g. see Duff et al., 1996, Nature, 383: 710-713, who teach that mice that

overexpress presenilin 1 (PS1) exhibit no phenotype). For an artisan, this means that the transgenic animal looks similar to the wild type control and cannot be used to compare differences between the wild type state of the animal and the state as a result of the transgene. The breadth of the claims, as written, encompasses transgenic non-human animals which have no phenotype. Neither the specification nor the art teaches an artisan how to use any transgenic non-human animals that exhibit no phenotype. For this reason, the specification does not enable the artisan to practice the claimed invention for its fullest breadth.

With regards to the Applicant's argument that the claimed invention encompass transgenic animals, wherein the animals lack a phenotype are usable by artisans as these animals can express a protein of interest in the milk of the animal (Applicant's response, page 10, section B), the Examiner does not find the argument persuasive. The reason for this is because while the specification indicates the idea on page 50, nothing in the specification teaches an artisan what proteins could be expressed in milk, nor was any guidance provided as to how one would obtain and purify the protein of interest from the milk. The art teaches that protein purification in not routine in the art as the purification of any protein is not carried out in a similar series of method steps. Rather, protein purification is an empirical process. The specification does not provide any guidance as to how one would obtain any protein secreted in the milk by transgenic animals. Further, the claims are not so limited and read broadly on the expression of any protein, including intracellular and transmembrane proteins which are not capable of being secreted.

With regards to the Applicant's response that the specification provides extensive guidance of how to prepare a transgenic animal comprising a transgene, as claimed (Applicant's response, pages 11-12, section C) the Examiner does not find the argument persuasive. The reason for this is because the focus of the Examiner's argument was not so much that the specification lacked the steps needed to generate a transgenic animal comprising the tet transgene system. Rather, the specification lacked guidance that teaches an artisan how to anticipate any phenotype using any transgenic non-human animal comprising the tet transgene system. This means that the specification has not taught an artisan how to anticipate all phenotypes (and lack of phenotypes) in all transgenic animals made by this system. The Examiner has pointed to the teachings of Hammer et al. who teach that not all heterologous transgene constructs will function similarly in all species of animals (e.g. see Office Action of July 8, 1999, page 4). For example, the Examiner has indicated that not all promoters and enhancer elements many not function in all species of animal because they may require specific cellular factors (Office Action, July 8, 1999, page 4, 2nd parag.). With regards to expressing a gene of interest, the art teaches that not all genes of interest have activity in heterologous animals. For example, Hammer et al., (1986, J. of Anim. Sci., 63: 269-278) teach that transgenic mice and pigs comprising a transgene comprising a nucleic acid sequence encoding human growth hormone (hGH) could express hGH mRNA (Hammer et al., 1986, page 274, under "Expression of mThGH Genes"). However, when determining whether transgenic animals responded to hGH, Hammer et al. teach that while transgenic mice responsded to hGH, the transgenic pigs did not (Hammer et

al., 1986, page 276, parag. under "Effect of Foreign GH on Growth"). Thus, with regards to the instant invention, nothing in the specification teaches an artisan how to overcome the teachings in the art, wherein an artisan could predict that expression of a heterologous gene of interest, driven by a promoter or enhancer of interest will result in a phenotype in any transgenic non-human animal, such that an artisan could detect a phenotype and use the animal. It would be undue experimentation for an artisan to determine the phenotypes for each transgene and each promoter and enhancer in every species of animal. It would also be undue experimentation for an artisan to know what are the parameters used to determine whether a transgenic animal would exhibit a phenotype when expressing a heterologous transgene and if that animal exhibited a phenotype, what the phenotype would be, as the specification and the art do not provide any guidance.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art of making and using transgenic animals at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Thus, for the reasons described above, while the specification enables an artisan to make and use a transgenic mouse comprising in its genome, a tTA expression construct comprising a nucleic acid sequence (SEQ ID NO. 1) encoding tTA^R operably linked to a CMV promoter and a luciferase reporter construct comprising a nucleic acid sequence encoding luciferase operably linked to a tetracycline-responsive P_{hCMV*} promoter (SEQ ID NO. 8), wherein luciferase activity was detectable in the seven

tissues of the double transgenic mice examined: pancreas, kidney, stomach, muscle, thymus, heart, and tongue, the specification does not reasonably provide enablement commensurate with the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54, 66, 71, 74 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54, 66, 71 are comprised of a list of silencer domain proteins. While the specification teaches ZF5, it does not teach what ZFS is.

Claim 74, step a, has the phrase, "a fusion protein which inhibits transcription of a in operator linked gene." It is unclear what this means.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M WEHBE' PH.D
PRIMARY EXAMINER